Nonylphenol ethoxylate(NPE) is a widely used surfactant and known hormone disrupter. In previous study, NPE is readily absorbed and rapidly removed from the body by gastrointestinal and renal excretion routes. P-glycoprotein(P-gp) that confers cellular multidrug resistance to many cytotoxic compounds may be an ideal candidate for this excretory role and can transport nonionic detergents like NPE. NPE similar to Tergitol NP-9 is identified in human urine. It was reported that high concentration of NPE might enhance the membrane transport due to cell membrane damage.However the effect of NPE on epithelial membranes is not yet studied in lower concentrations may be similar to the physiological level. In this study, the effect is examined using the Caco-2 and LLC-PK1 cell lines. TEER was also measured to know the effect of NPE on the tight-junction with EVOM.Caco-2 and LLC-PK1 cells were grown to confluency on a polycarbonate membrane inserts to permit loading of paracellular markers(mannitol and inulin), a transcellular transport drug(Ketoprofen), and P-gp substrates(Rhodamine 123 and Daunomycin) in the presence of NP-9 and other NPE. When NPE was put either in the apical or basal side, TEER was significantly decreased and the transport of mannitol, a paracellular marker, was increased and these changes were reversible in 2hrs. There was no significant change in the transport of Ketoprofen. P-gp induction by NPE pretreatment didn't affect the transport of P-gp substrates. In conclusion, the effect of NPE on the barrier function of epithelial membranes is not by P-gp induction but by tight junction opening.

[PE1-34] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Agitation condition does not affect the correlation between in vitro permeability and in vivo bioavailability of drugs.

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It has been well-known that a strong correlation is observed between in vitro permeability and in vivo bioavailability. But its curve was different in each labs. The permeability of drugs across Caco-2 cell monolayers have been measured and varied under each different agitation condition. Also there is a report that the permeability of some hydrophobic drugs were increased by the increasing rate of agitation. So we studied the effect of the agitation on the permeability of each drug and the relationship between the difference of Papp by the agitation(△Papp) and the hydrophobicity of drugs. Also we investigated the effect of △Papp on the correlation curve between in vitro permeability and in vivo bioavailability. The transport of drugs were examined under two different agitation condition(60 rpm, 0rpm, respectively) using Caco-2 cell monolayers.
As a result, permeability(Papp) of propranolol, phenylpropanolamine and YH-439 was slightly increased by the agitation. But, Papp of mannitol, cimetidine, ranitidine, hydrocortisone, loxoprofen, theophylline, tacrine and benzylpenicillin was not affected by the agitation. Also △Papp was not related with hydrophobicity of drug and the agitation didn't change the curve indicating the relationship between the permeability and the bioavailability.
In conclusion, it may not be necessary to consider the effect of agitation when we intend to predict in vivo bioavailabililty from the permeability of drugs across Caco-2 cell monolayer.

Poster Presentations - Field E2. Pharmacokinetics

[PE2-1] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Population pharmacokinetics of aceclofenac in Korean healthy subjects using NONMEM

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The purposes of this study were to assess the pharmacokinetics of aceclofenac in Korean using a population approach and to investigate the influence of characteristics of subjects such as body weight and age on that of aceclofenac. Plasma data from 156 Korean healthy male subjects who participated in several different bioequivalence studies of aceclofenac 100 ㎎ were used for this analysis. Plasma aceclofenac concentrations were measured using HPLC with UV detector. A 2-compartment model with lag time was fitted to the aceclofenac data using NONMEM. In result, population mean Cl/F, V_c/F, K_a, V_p/F, Q/F and T_{lag} were 4.37×10^3 ㎖/hr, 3.95×10^3 ㎖, 0.99 hr^{-1}, 9.60×10^3 ㎖, 1.02×10^3 ㎖/hr and 0.39 hr, respectively. Intersubject coefficient of variation (CV) ranged from 0.06 to 74.90% and residual intrasubject CV was 40.50%. A 2-compartment model with lag time was fitted well to the aceclofenac data, and there were no influence of age or body weight on fitting.

[PE2-2] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Validation of a high-performance liquid chromatographic method for the determination of YH3945 in rat plasma

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YH3945, a non-peptide farnesyltransferase inhibitor, is being developed by Yuhan Research Institute for the treatment of cancer. A sensitive and specific assay based on high perfomance liquid chromatography (HPLC) has been developed and validated for the determination of YH3945 in rat plasma. Plasma was extracted with acetonitrile containing the internal standard. An aliquot of the extract was injected onto a reverse C18 column. Retention times of YH3945 and the internal standard were 6.25 and 9.94 min, respectively. The chromatograms showed no endogenous peaks from blank plasma at the retention time of YH3945. Standard curves of YH3945 was linear over the range of 50 ng/ml to 5000 ng/ml (r=0.9998). The lower limit of quantification was 50 ng/ml using 100 ul plasma. This assay also showed good inter- and intra-precision and accuracy throughout the concentration range. YH3945 was stable for 72 hours in the sample extract, for 4 hours in ambient condition, for up to 14 days at frozen condition, and after exposure to three freeze/thaw cycles. This sensitive, accurate and precise method can be applied to determine concentration of YH3945 in plasma for pharmacokinetic studies in rats.

[PE2-3] [10/19/2001 (Fri) 09:00 - 12:00 / Hall D]

Population pharmacokinetics of clarithromycin in healthy adult Korean

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The purpose of this study is to estimate the population pharmacokinetics of clarithromycin in healthy adult Korean and to investigate the influence of various factors on the pharmacokinetics of clarithromycin.
The population pharmacokinetic parameters of clarithromycin were calculated with the data from the bioequivalance test. A total of 798 plasma concentrations from 78 subjects with single oral dose of 250mg or 500mg were used for the modeling. The concentration-time data were fitted to one-compartment open model with first-order absorption and elimination with no lag time using WinNonlin.